REMARKS

Claims 1-6, 9-10, 15, 21-27, 29-32 and 35-41 are pending in the application. Claims 28 and 33-34 have been canceled, claims 7-8, 11-14 and 16-20 are withdrawn, and claims 1, 6 and 40 have been amended.

Applicants were pleased to note that the Examiner has found claims 15, 31, 32, 35 and 36 allowable, and claims 40 and 41 allowable after amendment.

The Examiner has stated that claims 7-9, 11-14, 16-20, 29 and 37-39 have been withdrawn. Applicants note that previously, claims 7 and 8, 11-14 and 16-20 were withdrawn by the Examiner as directed to non-elected subject matter. In the last Action, the Examiner additionally withdrew claims 9 and 29 as directed to non-elected subject matter for being drawn to a method of determining if a compound binds to and increases the clearance of a low density lipoprotein using three distinct antibodies.

Applicants disagree with the withdrawal of claims 9 and 29 and ask the Examiner to reconsider withdrawal of these claims. Claim 9 is directed to a method to determine *if a compound causes a change in the structure of apolipoprotein B-100* in a low density lipoprotein by allowing the compound to bind with low density lipoprotein to form a complex, exposing the complex to an antibody on a solid phase to form a combination, detecting a second antibody that binds to the combination with a third antibody bound to a label, and quantifying the amount of captured combination and comparing it to a control. Applicants draw the Examiner's attention to the restriction requirement issued February 2, 2001. In response to this requirement, Applicants elected to prosecute claims to a method for determining whether a drug qualifies as an LDL-clearance enhancing drug by assessing its capacity to *change the three dimensional conformation of apolipoprotein B100 (apoB100).* Claims 9 and 29 are within the elected invention. Applicants request that the Examiner reconsider the withdrawal of these claims from consideration.

Rejections under 35 U.S.C. § 112

Claims 6, 10, 23-27, 30, 40 and 41 are rejected under 35 USC § 112 second paragraph as indefinite. The claims have been amended to promote prosecution.

The Examiner has rejected claim 6 for improper antecedent basis for "a lipoprotein receptor." Applicants have amended the claim to recite "the low density lipoprotein receptor," which has antecedent basis in the preamble of the claim.

Claim 30 was also rejected for lack of antecedent support in reciting "the cholesterol containing low density lipoprotein." Claim 30 has been amended to delete the phrase "cholesterol containing" to obviate this objection.

Claim 40 is rejected because it is allegedly unclear how the second antibody detects the combination in step (ii). The claim has been amended to overcome this objection. Applicants have amended the claim to indicate that the second antibody is added to the combination and the label is detected. The claim has also been amended to replace the phrase "captured in the assay" with "quantified in step (iv)."

Applicants believe these amendments overcome the Examiner's rejections under 35 USC § 112.

Rejections under 35 USC § 103

The Examiner has rejected claims 1-3, 6, 21-24, 27 and 30 under 35 U.S.C. § 103 as obvious in light of Somers (U.S. Patent No. 6,121,319). Claims 4, 5, 10, 25 and 26 are rejected under 35 U.S.C. §103 as obvious over Somers in view of Koren (U.S. Patent No. 6,107,045).

On page 4 of the Office Action, the Examiner characterizes the pending claims as drawn to methods "wherein a compound is administered to a human host to enhance clearance of

cholesterol-containing low density lipoproteins" (CC-LDL). The rejections put forth by the Examiner appear to rely on this characterization of the claims. Method of therapy claims are statutorily different than method of assay claims. A prior art reference disclosing a method of therapy does not necessarily disclose a method for screening compounds unless the screening steps are specifically disclosed in the prior art reference. Applicants agree with the Examiner that Somers teaches a method to treat a patient with the monosuccinic acid ester of probucol to lower LDL. Somers does not disclose the presently claimed assays.

Specifically, the pending claims are drawn to methods to assess whether a compound increases the binding affinity of a LDL to a LDL-receptor, potentially by causing a change in apoB100, and thus increases the clearance of the LDL.

To establish a *prima facie* case of obviousness, the following criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings; (2) there must be a reasonable expectation or success; and (3) the combined references must teach or suggest all the claim limitations.

The references do not teach the claimed invention. The present application discloses that certain compounds change the conformation of apoB100 and/or increase the binding of certain types of LDL to LDL receptors. There was no suggestion in the prior art that this mechanism could be used to test whether compounds could be effective in enhancing LDL clearance.

As the Examiner has pointed out, several claims are even drawn to *in vitro* methods of assessing the binding between LDL and its receptor. There is no suggestion of *in vitro* assays that test how compounds affect the binding of LDL to the receptor in the art cited by the Examiner. In fact, the only methods described test the *total levels* of LDL in blood (see Examples 5 and 8, showing the effects of these compounds by 1) administering the compounds and 2) observing the effects on total cholesterol and CC-LDL). That is not the assay recited in the claims.

These method of assay claims are not taught by Somers alone or in combination with Koren because neither Somers nor Koren either identified, taught, or discovered this assay. The amended claims are directed to methods to determine whether a compound will enhance the clearance of a LDL in a host (claims 1, 6 and 37), or bind to and change the structure of apolipoprotein B-100 (claim 9). Specifically, claim 1 is directed to a method of assessing whether a compound can bind to an enhance clearance of a CC-LDL by administering the compound to a host, determining whether binding has occurred between the compound and CC-LDL from the host, thus forming a complex; and determining whether the complex results in a change in the binding affinity of the CC-LDL to the LDL receptor. There is no suggestion in the cited references to assess binding as recited in the claims.

In the method of claim 6, a compound is mixed with the LDL and the method includes determining whether the compound binds to the LDL and forms a complex; and determining whether the complex alters the three dimensional conformation of the LDL such that the binding of the LDL to the LDL receptor is enhanced. There is no suggestion in the applied references to assess the specific binding activity of a compound as claimed. Similarly, there is no suggestion of the specific method of detecting the effects of a compound on the conformation of a CC-LDL in general or apolipoprotein B-100 specifically that enhances the affinity of the low density lipoprotein for its receptor.

There is no suggestion in the references to evaluate the effect of compounds on binding of LDL to its receptor by conformation changes they induce on LDL. As stated on pages 13-14 of the application, prior to this discovery, it was not known that serum cholesterol can be lowered by a compound that intercalates into CC-LDL to increase binding to LDL-receptors. The present claims are directed to methods of assessing binding properties of a compound in an *assay*. Somers provides no teaching or suggestion of the claimed methods of assessing binding properties of compounds that act to lower LDL levels. From the disclosure of Somers, there would have been no suggestion to assess the particular binding properties in the methods recited in the claims.

One of ordinary skill in the art would also not have been motivated to combine disclosure in Somers with that of Koren to obtain the methods recited in the pending claims. Somers provides no suggestion that compounds operate to lower LDL levels by changing the binding affinity of LDL for its receptor. Koren discloses assays directed to quantifying the *amount of lipoproteins* present in a sample of blood. Koren does not teach or suggest determining the effects of a compound on binding of LDL to an LDL receptor. There would not have been any motivation to modify the assays of Koren to screen for active compounds because the methods of Koren do not teach or suggest anything to screen for other than blood levels of lipoproteins. The claimed methods rely on a mechanism of action not disclosed or suggested in the applied references. Therefore, there would have been no motivation to assess the binding properties discovered by the Applicant as useful to assess and determine activity of a compound.

In summary, neither Somers nor Koren teach or suggest the specific methods defined by the limitations of the claims. Withdrawal of the rejection under 35 U.S.C. § 103 is therefore respectfully requested.

Conclusion

In view of the above presented amendments and arguments, Applicants request that the Examiner allow the pending claims. Applicants enclose a check for $440.00 for a three month extension of time. The Commissioner is hereby authorized to charge any additional fees associated with this response to Deposit Account No. 11-0980.

Respectfully submitted,

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